CSIS HIV/AIDS TASK FORCE

# Expanding Antiretroviral Treatment in Developing Countries Creates Critical New Challenges

**Project Director**
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## Preface and Acknowledgments

The CSIS Task Force on Strengthening U.S. Leadership on HIV/AIDS is cochaired by Senators Bill Frist (R-Tenn.) and John Kerry (D-Mass.) and is funded by the Bill and Melinda Gates Foundation and the Catherine Marron Foundation. Undertaken in collaboration with the Centers for Disease Control and Prevention and the U.S. Agency for International Development, the task force will outline strategic choices that lie ahead for the United States in fighting the global AIDS pandemic. The task force seeks to build bipartisan consensus on critical U.S. policy initiatives and to emphasize to senior U.S. policymakers, opinion leaders, and the corporate sector the centrality of U.S. leadership in strengthening state capacities in Africa and India to enhance prevention, care, and treatment of HIV/AIDS. J. Stephen Morrison, director of the CSIS Africa Program, manages the overall project.

The CSIS Task Force comprises an eminent persons panel and a broader working group. The eminent persons panel is drawn from Congress, the administration, public health groups, the corporate sector, activists, and others. The panel will help shape the direction and scope of the task force and disseminate findings to a broader U.S. audience. Expert working-level committees focus on strengthening global financing and coordination mechanisms; counteracting the destabilizing consequences of AIDS; extending training and elementary infrastructure to enhance prevention, treatment, and care; discerning and shaping public opinion on global HIV/AIDS; and defining the resource and capacity requirements for effective U.S. leadership in fighting the pandemic.

This paper is a product of the task force's committee on capacity building. J. Stephen Morrison, director of the task force, managed a collaborative drafting process, which incorporated substantial input and technical guidance from Phillip Nieburg of the Centers for Disease Control and Prevention, James O'Brien of the Albright Group, Todd Summers of Progressive Health Partners, Nancy Bearg Dyke, consultant, and Jennifer Cooke, deputy director of the CSIS Africa Program.

# Expanding Antiretroviral Treatment in Developing Countries Creates Critical New Challenges

*J. Stephen Morrison*

## Introduction

In the face of a swiftly expanding global HIV/AIDS pandemic, world opinion has shifted significantly in favor of providing access to antiretroviral treatment (ART) in developing countries. Treatment is now seen as a critical component of a comprehensive program against HIV/AIDS, along with prevention and the improvement of health care infrastructures for the delivery and monitoring of care. Indeed, more than half the programs approved by the Global Fund to Fight AIDS, TB, and Malaria in its first round of approvals call for funding for such treatment.

Until recently, that goal had not seemed feasible. High costs, demanding treatment regimens, and the lack of even basic health infrastructure in many heavily affected regions were all cited as potentially insurmountable barriers.

But then the "Call to Action" enacted at the June 2001 UN General Assembly Special Session on HIV/AIDS pushed forward a new global consensus on the need for ART. At the same time, pressure from various sources led many pharmaceutical manufacturers to reduce drug prices dramatically. Publicity about Brazil's national ART distribution program added to the public discussion, and the December 2001 release of a report by the Commission on Macroeconomics and Health, authorized by the World Health Organization (WHO), proposed practical approaches to resolving problems of price and productive capacity of industry and developing effective delivery infrastructure, especially in countries much poorer than Brazil. More recently, in late April 2002, the World Health Organization released guidelines for antiretroviral use in poor countries, added 10

of the drugs to its list of "essential medicines" for all countries, and for the first time qualified a number of generic manufacturers. That same week, the Global Fund allocated its first round of grants to 58 country programs, of which 31 included some HIV/AIDS treatment. Several developing countries with large and increasing burdens of HIV/AIDS are now beginning public-sector acquisition and distribution of ART drugs.

ART programs in developing countries are relatively small today but are expected to grow dramatically in the next few years. At present, an estimated 250,000 people in the developing world receive ART. Only 30,000 persons are on ART in Africa, where 28 million are infected with HIV and an estimated 5 million suffer from AIDS. The WHO has set a goal for 2005 of having 3 million persons in the developing world on ART—a 12-fold increase in less than four years. Much of that increase is intended to come in Africa and other resource-limited settings with weak health infrastructures.

This paper examines the downstream implications of this new commitment to provide ART to people living with HIV/AIDS in developing countries. Specifically, what new challenges are likely to emanate from expanded treatment programs that reach large numbers of HIV-infected persons? And what policy and programmatic innovations will be needed to address these challenges?

Six core challenges are emerging as HIV-treatment programs expand:

- Substantially more resources are required to expand health system capacity. Most essential will be training the people who will implement prevention, care, and treatment programs.
- ART regimens must be made even more affordable.
- Priority prevention activities must be strengthened and better integrated with treatment.
- The adverse side effects of ART must be anticipated and mitigated.
- The emergence of antiretroviral drug resistance must be anticipated and mitigated.
- Capacity must be rapidly developed to meet the needs of a growing population of people living with HIV/AIDS.

## Critical Challenges

### *1. Substantially more resources are required to expand the capacity of health systems to address HIV/AIDS. Most essential will be training the people who will implement prevention, care, and treatment programs.*

Large-scale increases in HIV/AIDS care, treatment, and prevention programs will require proportionate investments in creating host-country capacity—facilities, equipment and supplies, and most importantly, investment in the training of people. More clinics and trained staff will be needed to carry out counseling, treatment, prevention, and care activities, and more laboratory

capacity will be needed for HIV testing itself as well as for diagnosing opportunistic infections, drug resistance, and adverse effects of ART.

As just one specific example of needs along a treatment continuum, before receiving ART, persons must be identified as HIV infected and as having met other medical or public-health selection criteria. However, public-sector counseling and testing (CT) programs to identify and counsel large numbers of HIV-infected persons are not yet widely available in many countries. In addition, where CT programs do exist, the capacity to make or confirm an HIV diagnosis or clinical AIDS diagnosis or to conduct other appropriate laboratory testing is often limited. Until CT programs are more widely available, many HIV-infected persons who could benefit from ART and other interventions (for example, counseling itself) may not be identified until later in the course of illness (when ART may be less effective) or not at all. Expansion of CT programs is thus an urgent need in countries intending to reach substantial proportions of their HIV-infected populations. Large numbers of trained people will be needed to carry out these CT program functions to further both treatment and prevention goals.

In sum, the demand for investment in people to create a diversity of human skills is increasing dramatically, as treatment expands. At present, however, it is unclear how much investment will be required, whether present investment levels are sufficient (they appear insufficient), and how the training of a large skilled and semiskilled workforce to run multiple programs in each affected country will be achieved in an orderly, phased, and sufficiently comprehensive manner. While there is an awareness that investing in people is the sine qua non of success, there is considerable confusion and uncertainty surrounding training requirements and how to allocate resources for those requirements.

An immediate imperative is to stabilize and replenish the existing human-resource base that provides health care in Africa and other acutely affected developing countries. In many countries, that base is under siege. Health providers themselves are getting sick at high rates, and many who are healthy are migrating to more remunerative and less stressful opportunities in Europe, North America, and elsewhere. How to stem these destabilizing attrition rates is as yet poorly understood, and there are only a few pilot stabilization programs that invest on an urgent basis in the critically important personnel who are already working—but at risk of getting sick or leaving.

Second, not enough work has been done thus far, at a global or country level, to define with precision what types of personnel will be required as programs are brought to scale and at what cost. Few countries, in their national plans or in their submissions to the Global Fund, have laid out systematically their projected human-resource training needs. In the future this is one area where the Global Fund can, and should, press for more informed planning and budgeting.

Key donor countries and international institutions are similarly vague about projected training needs and how to answer them.

For example, even U.S. government agencies involved in HIV-control efforts have a hard time saying with any specificity what proportion of their current

annual expenditures on international HIV/AIDS is dedicated to training. No donor or international agency has issued an informed estimate of future training requirements for countries now affected by HIV/AIDS or those at risk of an expanding epidemic. No agency has seriously analyzed the cost-effectiveness of different training models, the capacities of Africa's network of medical and public-health training institutions, and the potential for strengthening those institutions.

Several different models for investing in people have been tabled. French health minister Kouchner has advocated the "twinning" of northern and southern health institutions, an idea endorsed by the United States and several EU members states. Some U.S. officials advocate building out incrementally from existing research networks and developmental programs created by agencies such as the U.S. National Institutes of Health, the U.S. Agency for International Development, and the Centers for Disease Control and Prevention. Others have advocated empowering the Health Resources Services Administration at the U.S. Department of Health and Human Services to take a lead role in training overseas; the creation of an American health corps to work overseas for several years; and new pedagogical models appropriate to emergency situations that shorten and simplify training approaches, allow for the training of sufficient staff to account for future illness, and concentrate the agenda of health institutions on select core priorities.

The future will require a far greater and more coherent investment in training people in HIV-affected countries around the world. It will require a two-pronged approach that stabilizes health systems while building up additional capacities and finding the means for these personnel to have sustainable careers. Very likely, a multiplicity of approaches will be pursued and enlarged. The urgent need is to quantify requirements, including reasonable salaries and other costs; forge a coherent, phased strategy informed by realistic estimates of future demand for training; establish principles for training that emphasize skills transfer and local capacity development; and clarify which primary instruments and budget lines the United States will use to invest in people as demand for skills expands dramatically in the future.

### *2. ART regimens must be made even more affordable and sustainable.*

While significantly below industrialized country levels, the price of antiretroviral drugs in many HIV-affected countries is still in the range of $600 to $1,000 per person per year. This price remains a significant barrier to providing ART to the many people who need it. Additional costs, such as creating and staffing CT and other needed HIV-control programs, must also be covered. Success will depend on further reductions in the price of ART and related interventions to a point where they become affordable for a larger proportion of an ever-growing population of people living with HIV/AIDS.

Improved treatment for HIV-positive individuals hinges on assurances of affordable, sustainable increases in the availability of drugs, combined with long-term investments in improving the infrastructure needed to deliver care, including

drugs, effectively. The Global Fund is in a position to shape a global arrangement that would provide, over time, adequate supplies of treatments, and innovative new treatments, in a system that could assure planners that drugs would continue to be available.

The nub of the approach has been laid out in the report of the Commission on Macroeconomics and Health to the WHO, in a section authored by the executive director of the Global Fund, Dr. Richard Feachem. In essence, the fund could broker an arrangement in which the pharmaceutical industry commits itself to making medicines available in sufficient numbers, at low but profitable prices as decided in each market. This arrangement, although brokered by the Global Fund, should be endorsed by trade ministers, who would make clear that the flexibility inherent in intellectual property provisions would be used if the industry failed to make sufficient, affordable supplies available. Such an arrangement would provide market incentives, the surest means to keep supplies available, enforced by an unequivocal commitment by trade ministers.

The Global Fund must be diplomatically active to carry out this initiative. The next ministerial of trade ministers, scheduled for September 2003, provides a feasible and important target date for efforts to seek endorsement. A crowded diplomatic calendar in the meantime, in the UN, the World Trade Organization, and various specialized agencies, will require diligence and a clear message from the fund in order to bring all interested parties to agreement. The fund will need a senior diplomat on staff to carry out this demanding task. Major donors to the fund will also need to provide technical assistance and ongoing, senior-level diplomatic support for this effort if the fund—with a deliberately streamlined staff—is to manage this difficult task.

### *3. Priority prevention activities must be strengthened and better integrated with treatment.*

Providing equitable access to ART for HIV-infected persons is a critical goal for HIV-control programs. However, the ultimate solution to the global HIV pandemic, as well as to HIV epidemics within individual countries, rests overwhelmingly with effective prevention of new infections.

Some overlap does exist between HIV-prevention and treatment programs, and access to treatment provides an important incentive for people to respond positively to prevention campaigns by being tested and, if infected, seeking care. In addition, preventing subsequent HIV transmission by those identified as infected is an important goal. Nonetheless, the target populations (infected vs. uninfected people), goals, activities, and necessary staff skills for treatment and prevention activities are largely different. It is a stark truth that, no matter how far drug prices fall and no matter how widely ART access is provided, even a highly effective HIV-treatment program will not guarantee success in preventing future HIV infections. Even in the United States, with near universal access to ART, the estimated level of new HIV infections was not demonstrably affected by the introduction of highly active ART in the late 1990s.

In fact, there is some evidence that awareness of ART programs may inadvertently invite or encourage high-risk behavior. For example, patients receiving ART may increase their sexual activity as they begin feeling better in the mistaken belief that, since they no longer feel sick, they are no longer infectious. Such patients will need intensive counseling to reduce their risk of transmitting HIV to others, and the success of such prevention efforts will need evaluation. As another example, the U.S. experience suggests a risk of reversion to high-risk behaviors in some populations when use of ART becomes generalized. ART does lower blood levels of HIV enough to perhaps reduce the "per contact" biologic risk of HIV transmission to sexual partners. However, data on both rates of unsafe sexual practices and increases in rates of HIV and other sexually transmitted diseases since the advent of ART suggest that, at the population level, these behavioral backsliding effects could outweigh the beneficial prevention impacts of ART. In populations being provided with access to ART, it will be important to communicate to both HIV-infected and uninfected persons that these drugs do not cure HIV and are not an appropriate substitute for primary prevention.

How these factors will play out in various countries and cultures is unknown. A potentially negative impact of access to ART on the number of new HIV infections in developing countries needs to be studied and addressed systematically, as warranted, through new interventions.

*4. The adverse side effects of ART must be anticipated and mitigated.*

A large number of ART-related adverse effects of varying severity have been documented in the United States and other industrialized countries. Although these adverse effects may vary with the class of drugs and with specific individual drugs, many are thought to have a direct or indirect impact on treatment outcomes and quality of life. A direct adverse outcome may occur, for example, if a drug causes death or other severe health outcome, or if it leads to a person being taken off ART. An indirect adverse effect may occur if an adverse effect leads to a person becoming less adherent to a treatment regimen.

A few examples of adverse effects include those noted in the following table.

| Adverse Effect | Comment |
|---|---|
| Anemia | Most common with zidovudine (AZT); associated with lower survival; background anemia is common in developing countries, especially where malaria is endemic. |
| Fat Distribution Abnormality | Studies show a wide range of occurrence (6–80 percent) in ART recipients; associated with disfiguring body fat changes and adverse social consequences. |
| Liver Cell Damage (hepatotoxicity) | Most likely occurs with long-term use of nevirapine but seen with most drugs; may occur more frequently in persons co-infected with hepatitis B or C. |
| Lactic Acidosis | Rare (<0.2 percent of treated persons) but fatal in one-third of affected persons. |

Although most adverse effects may occur at low frequency, the very large numbers of persons to be treated means that many individuals could be affected. In addition, it is not yet known if these or other adverse effects will occur in developing country populations more or less frequently than U.S. or other industrialized country populations. Differences in diet, environment, or physiology may be important factors. Whatever their ultimate patterns, the population-level occurrence of ART-related adverse effects will need to be monitored at least initially in new populations taking ART, and their occurrence in individuals needs to be anticipated and planned for. In order to minimize lack of adherence due to direct adverse effects, persons taking ART should be counseled in advance about these effects so their occurrence is not totally unexpected.

### *5. Antiretroviral drug resistance will develop—the question is how to contain it.*

As ART comes into wider use in developing countries, the rapid evolution of the HIV genome ensures that drug-resistant virus strains will emerge, just as they have in industrialized countries. Drug resistance is likely to occur most rapidly among people who do not adhere well to their ART regimen, although it can sometimes also develop among people who are highly adherent. Emergence of drug resistance will also occur as more individuals become infected from a virus pool in the general population that contains a rising percentage of ART-resistant strains, since people "inherit" the resistance pattern of the HIV strain that infects them.

Over time, an unknown but probably significant proportion of persons eligible to receive ART will develop or acquire HIV strains that no longer respond well to current ART. In the United States and other industrialized countries (where 10–25 percent of persons on ART have developed or acquired some degree of drug resistance), the recommended response is to change ART regimens and substitute or add new drugs to which the virus has not yet developed resistance. These changes often require complex and expensive genetic testing of the virus to better identify resistance patterns. In developing countries, where a smaller number of ART drugs are likely to be available and where sophisticated genetic testing is unavailable, access to alternative regimens will therefore be restricted.

Containing drug resistance in expanding ART programs is best achieved through heavy emphasis on supporting patient efforts to adhere to their treatment regimens, including

- careful examination of cultural factors influencing adherence;
- intensive individual counseling that takes account of local culture;
- providing patients with realistic expectations of adverse effects of ART; and

- ongoing community-level support. Effective systems for monitoring development of drug resistance at population levels will be essential in all places where ART comes into wide usage.

*6. Capacity must rapidly be scaled up to meet the needs of a growing population of HIV-infected people.*

The number of HIV-infected people in the world continues to grow at a rapid rate, leading to ever-greater resource requirements. To the extent primary prevention efforts are weak or ineffectual, the number of new infections will grow even faster. In addition, as successful ART programs reduce or delay mortality among HIV-infected persons, populations will contain ever-larger numbers of HIV-infected people.

Some HIV-infected persons may not have access to ART because they live in places where ART programs are not yet widely available or because they are too ill when identified as infected to benefit from ART. Others, begun on ART, may eventually have treatment discontinued—for example, persons unable to tolerate ART's side effects; persons who develop drug resistance and run out of alternative antiviral treatment options; or persons who clearly do not adhere to their regimen. Finally, because ART slows progression of HIV/AIDS but does not cure HIV infection, still other people will have their HIV/AIDS disease progress despite ART.

Many people in each of these various groups will eventually get sicker and will need appropriate care. It is important to begin now to plan systematically for these eventual increases in numbers of persons living with HIV, many of whom could benefit greatly from health and social services. The capacity of the pharmaceutical industry, both generic and research based, to produce sufficient amounts of complicated treatment regimens in the necessary quality, and at sufficiently low prices, will be greatly tested. Current approaches, including philanthropy, pledges not to seek profit in the poorest countries, or very low-cost alternatives to sophisticated products, all raise serious questions about the reliability and sustainability of production needed for adequate long-term planning. Practical proposals, including adequate incentives to sustain the research needed to stay ahead of the disease (see challenge five), as proposed by the Commission on Macroeconomics and Health, will need serious consideration. Persons who are not able to receive ART, or whose ART is stopped, need to be referred to programs where they can still receive supportive care. Policymakers need to anticipate the increasing need to elaborate programs of home-based and community-based palliative care for terminally ill persons.

## Conclusions

As antiretroviral treatment expands in developing countries, critical challenges are emerging that call for a new action agenda by the United States, other donors, and international organizations. New models for delivering care, prevention, and treatment need to be developed.

First, within any specific country or other administrative unit, HIV-prevention, HIV-care, and HIV-treatment programs and services need to be considered as a single comprehensive strategy with complementary and mutually reinforcing activities.

Second, it is essential to spotlight investment in developing new capacity and supporting existing capacity to carry out the work. This requirement means devising programs to stabilize weakened institutions, expand personnel levels, and curb attrition rates among already qualified professionals. It means coordinating the activities and planning of the Global Fund, UN agencies, U.S. bilateral agencies, and others to clarify present and future demands for training, including costs. And it means defining an integrated U.S. capacity-building strategy and clarifying budgetary lines for heightened U.S. commitments.

Third, increasing access to HIV/AIDS medicines will increase the need for sustained international leadership. Trade ministers, for example, must convince companies to provide affordable access voluntarily, in return for assurances on differential pricing and protection against diversion of low-cost drugs into lucrative markets.

Fourth, if treatment is to be more effectively linked to prevention, if side effects of ART are to be humanely managed, and if adherence is to be emphasized as a tool for containing drug resistance, far higher priority needs to be given to intensive counseling of patients receiving ART. The need for prevention support does not stop with the introduction of ART; on the contrary, it increases.

Finally, serious planning needs to begin now to anticipate correctly the needs of increasing numbers of HIV-infected people. Alternatives such as home- and community-based care for sick individuals and community support for impacted families need to be considered, tried, and evaluated.